Managing Myeloma

Monotherapy GSK2857916, an Anti-BCMA Antibody in RRMM

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Welcome to *Managing Myeloma*. I am Dr. Adam Cohen and I am live at the ASH Annual Meeting in Atlanta, Georgia. Today, I will review the preliminary results from part 2 of a first-in-human study using the antibody-drug conjugate GSK2857916 in patients with relapsed and refractory multiple myeloma. This is an antibody-drug conjugate that targets a protein called BCMA, or B-cell maturation antigen. To give a little bit of background, BCMA is a cell surface receptor that is highly expressed on both normal and malignant plasma cells. Its primary purpose is to maintain plasma cell homeostasis and long-lived plasma cell survival, and it does have a pathogenic role in myeloma, providing a signal to resist apoptosis and improve proliferation. This makes it a rational target for myeloma therapy. GSK2857916 is a novel anti-BCMA antibody that has been conjugated through a protease-resistant linker to a microtubule-disrupting agent called MMAF. This is a potent chemotherapy agent that induces cell cycle arrest. The primary mechanism of action of this antibody-drug conjugate is internalization of the molecule, cleavage of the linker and release of the MMAF within the tumor cell, leading to tumor cell death. In addition, the Fc portion of the antibody has been enhanced to improve binding to Fc receptors on innate effector cells such as NK cells and monocytes, and this leads to enhanced antibody-dependent cellular cytotoxicity (ADCC). The third potential mechanism is induction of an immunogenic cell death and stimulation of an endogenous antimyeloma response. There are multiple potential ways this drug can target myeloma. Preclinical studies demonstrated significant in vitro activity both against myeloma cell lines and primary patient myeloma samples, as well as significant in vivo activity in myeloma xenograft models. This provided the preclinical rationale to go forward in the clinical testing.

Study BMA117159 is a first-in-human phase 1 study. It is industry-sponsored and taking part at multiple centers. There are two parts to the study. Part 1 was a dose escalation, starting at very low doses and escalating up to 4.5 mg/kg, and part 2 was a dose expansion at the recommended phase 2 dose. The drug is given as a 60-minute IV infusion once every three weeks, and the study planned to give up to 16 cycles of treatment. The patient population targeted were patients with relapsed and refractory myeloma with prior exposure to an alkylating agent, proteasome inhibitor and IMiD, and patients had to be refractory to the most recent therapy. We presented part 1 (the dose escalation portion) of the study at last year's ASH: 38 patients were enrolled, there was no dose-limiting toxicity noted, and escalation proceeded all the way up to the maximum planned dose of 4.5 mg/kg. However, based on the totality of the toxicity data as well as pharmacokinetic and pharmacodynamic data, a dose of 3.4 mg/kg was chosen to go forward into the part 2 or dose expansion. At this year's ASH, we have recorded data on 35 patients who have been enrolled in part 2 at the recommended dose of 3.4 mg/kg. These were fairly heavily pretreated patients: 57% had five or more prior lines of therapy, 89% of subjects were dual refractory to at least one proteasome inhibitor and IMiD, and about a third of the subjects were refractory to daratumumab as well.

The primary objective of the study for the part 2 portion was the objective response rate. The primary objective overall of the study was safety and tolerability.

In terms of adverse events, the most common adverse events seen were thrombocytopenia as well as corneal toxicities. The thrombocytopenia was generally reversible and did not appear cumulative over time. The ocular toxicity was actually expected and there is a known toxicity of MMAF, the payload that is attached to the antibody. To try to mitigate against this, all subjects received steroid eye drops for four doses around each dose of the study drug. Despite this, however, 63% of subjects in the part 2 portion of the study developed some form of ocular toxicity. This manifested primarily as dry eye, blurry vision or photophobia, in some cases eye irritation, and objective findings could include keratitis or signs of corneal epithelial damage. This was grade 1 or 2 in all but three of the subjects who developed it, and it was reversible in the vast majority of cases. The median duration of corneal toxicity was about 30 days, and subjects could be re-treated following a dose delay and reduction of the dose, and therefore were able to stay on the study.

In terms of efficacy, the overall response rate was 60% in the 35 patients treated in part 2; 51% achieved very good partial response (VGPR) or better, three subjects achieved a complete response (CR) or a stringent CR, and the median duration of response is about eight months. The median progression-free survival (PFS) is not reached, and so this was actually fairly promising efficacy for a single agent in this heavily pretreated population of multiple myeloma.

The conclusion from this study is that this drug does have single-agent activity, it validates BCMA as a good target in multiple myeloma, and that this approach with the antibody-drug conjugate may have significant activity. I think some of the challenges remaining are figuring out ways to mitigate the corneal toxicity. There are efforts to use additional prophylactic measures to try to limit this, as well as potential additional treatments such as increasing the duration of steroid eye drops. The next steps are to proceed forward with a larger multicenter phase 2 study for a potential registration path, and the FDA has granted this drug breakthrough status. There are also additional studies that are being planned in combination with other standard myeloma agents such as IMiDs and proteasome inhibitors, and those will hopefully come online sometime later in 2018.

One of the other key points about this antibody-drug conjugate is that the infusions are very well-tolerated. There were grade 1 or 2 infusion reactions seen in about a quarter of patients; this was seen only in the first cycle and of note, no premedication was mandated during the first cycle. There were no significant infusion reactions seen with subsequent cycles and no patient had to discontinue treatment due to an infusion reaction.

Those are the key takeaways from this study and I would like to thank you for viewing this activity.

Reference:

Trudel S, Lendvai N, Popat R, et al. Deep and Durable Responses in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (MM) Treated with Monotherapy GSK2857916, an Antibody Drug Conjugate Against B-Cell Maturation Antigen (BCMA): Preliminary Results from Part 2 of Study BMA117159. ASH 2017. Abstract 741.